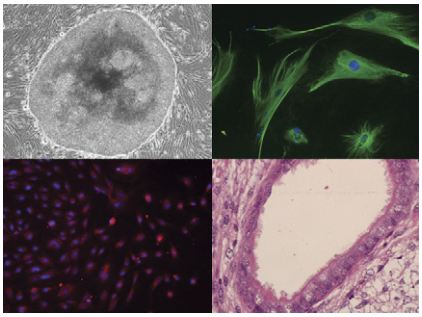
In This Issue

Pluripotent Stem Cells from Human Somatic Cells



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Shinya Yamanaka and coworkers previously reported the generation of pluripotent stem cells from mouse fibroblasts by transduction of four transcription factors: Oct3/4, Sox2, Klf4, and c-Myc. Yamanaka and colleagues (Takahashi et al.) now report the generation of pluripotent cells from adult human fibroblasts using the same four factors. These induced pluripotent stem (iPS) cells are similar to human embryonic stem cells in morphology, proliferation, marker expression, epigenetic status, and the ability to differentiate into cells of the three germ layers. Further, the authors show that, similar to embryonic stem cells, iPS cells can differentiate into neural and cardiac cells. This work demonstrates that pluripotent stem cells can be created from human somatic cells and opens the door to the generation of patient- and disease-specific stem cells.

A Ubiquitin Ligase Links DNA Damage Recognition and Repair

PAGE 901

In response to DNA double-strand breaks (DSBs), cells enhance the efficiency of genome surveillance by modifying histones near the DNA breaks, which serves to assemble protein complexes required for signaling and repair. Two papers by Huen et al. and Mailand et al. now report the identification of a ubiquitin ligase, RNF8, which accumulates at DSBs and ubiquitylates histones H2A and H2AX in response to DNA damage. RNF8 binds to phosphorylated MDC1, an early response protein, and recruits the repair proteins 53BP1 and BRCA1 to the damage site. RNF8 therefore integrates protein phosphorylation and ubiquitylation signaling at the DNA-damage site.

Cell-Cycle Delay due to tRNA Traffic Jam

PAGE 915

In order to maintain the fidelity of genetic information, organisms have evolved surveillance mechanisms that monitor the integrity of the chromosomes. Ghavidel et al. now show that in response to DNA damage, unspliced tRNA is accumulated in the yeast nucleus. There, it signals to upregulate the Gcn4 transcription factor, which causes a delay in upregulation of the cell-cycle regulator Cln2 and a G1 cell-cycle arrest. This report provides evidence that distinct cellular processes, such as nuclear/cytoplasmic tRNA transport, DNA damage, and cell-cycle arrest are functionally interconnected.

Ribosomal Protein Lends Specificity to NF-κB

PAGE 927

NF-κB is a well-known transcription factor complex that regulates numerous genes involved in inflammation, apoptosis, cell growth, and differentiation. The complex has been thought to function as a heterodimer of Rel proteins, such as p50 and RelA (p65). Wan et al. now demonstrate that Ribosomal Protein S3 (RPS3) is a previously unrecognized RelA-binding subunit that accounts for the greater size and affinity of certain natural NF-κB complexes compared to Rel heterodimers. NF-κB stimuli caused recruitment of RPS3 as part of the NF-κB complex to a specific subset of target genes. These observations provide insight into how NF-κB selectively controls gene expression.

Trex1 Extinction Triggers DNA-Damage Checkpoint and Autoimmunity

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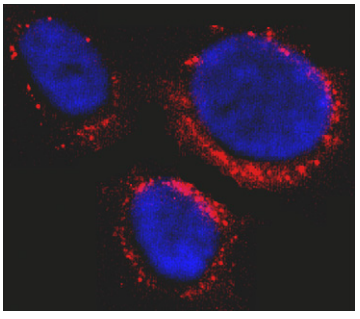


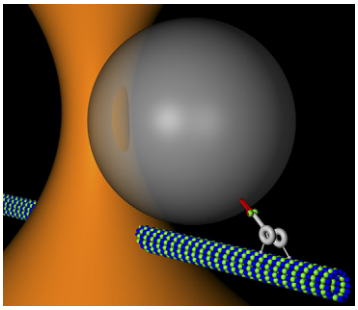
Inactivation of the Trex1 DNA exonuclease is associated with human autoinflammatory disease in Aicardi-Goutières syndrome. Yang et al. now report that in Trex1-deficient cells, persistent single-stranded DNA correlates with chronic activation of ATM-dependent DNA-damage checkpoint signaling. The authors find that Trex1 is responsible for the degradation of DNA molecules that originate during DNA replication. If not degraded, this previously unrecognized DNA species accumulates outside the nucleus and provokes an antiviral-like autoimmune response, characteristic of diseases linked to Trex1 deficiency.

The ABCs of CFTR Regulation

PAGE 940

Cystic fibrosis transmembrane conductance regulator (CFTR) is a cAMP-regulated chloride channel that exists as a macromolecular complex with a variety of signaling and transporter molecules. Here Li et al. identify the multidrug resistance protein 4 (MRP4) as a regulator of CFTR. MRP4, an ABC transporter that regulates cAMP transport, binds directly to CFTR and regulates its activity. This interaction between CFTR and MRP4 has important implications for secretory diarrhea and inflammatory bowel disease.

Dynein's First Nucleotide-Independent Steps



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Cytoplasmic dynein is a minus-end-directed microtubule motor whose stepping mechanism remains poorly understood. Using optical tweezers, Gennerich et al. examine the force-dependent stepping behavior of yeast cytoplasmic dynein. An opposing force induces more frequent backward stepping by dynein, and the motor walks backward at loads above its stall force. Remarkably, in the absence of ATP, dynein steps processively along microtubules under external load with less force required for minus-end than for plus-end-directed movement. This nucleotide-independent walking reveals that force alone can drive microtubule detachment-attachment cycles of dynein's motor domains, and the results suggest a model for how dynein's two motor domains coordinate their activities during normal motility.

Cells Out of Touch Get Eaten Alive

PAGE 966

Epithelial cells require attachment to extracellular matrix to suppress an apoptotic cell death program called anoikis. Now Overholtzer et al. have discovered a nonapoptotic cell death mechanism, which can eliminate cells deprived of matrix attachment. The authors find that deattached breast cancer cells appear to swallow one another, which can result in nonapoptotic cell death or release of the swallowed cell. This process, termed entosis, is evident by ''cell-in-cell'' structures similar to those reported in human tumors. The authors raise the possibility that entosis could serve as a mechanism of tumor suppression.

GSK3 Puts a Stop to the Smad-ness

PAGE 980

In *Xenopus* embryos, dorsal-ventral patterning is controlled by a gradient of BMP/Smad1 signals and the anteroposterior axis by a Wnt gradient. Fuentealba et al. now describe a new branch of the canonical Wnt pathway that regulates the duration of the BMP/Smad1 signal. This is achieved through the action of Wnt signaling on GSK3, an enzyme that phosphorylates and promotes the proteasomal degradation of Smad1 in the centrosome. Thus, BMP/Smad1 and Wnt patterning gradients are integrated at the level of Smad1 phosphorylation during embryonic pattern formation.

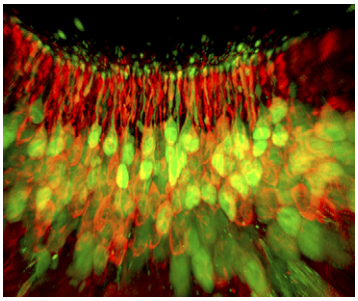
Hematopoietic Stem Cells on Border Patrol

PAGE 994

Hematopoietic stem and progenitor cells (HSPCs) constitutively migrate from the bone marrow into the blood, but the fate and functional relevance of circulating HSPCs is largely unknown. Massberg et al. now show that once in the blood, HSPCs traffic constitutively to multiple peripheral organs where they remain for at least 36 hr prior to entering the draining lymphatics to return to the blood. When HSPCs encounter bacterial products during tissue transit, they divide locally and give rise to dendritic cells. Hence, peripheral organs are constitutively surveyed by HSPCs that are highly versatile and can respond rapidly to distress signals from the local microenvironment.

Allelic Exclusion: Making an Either OR Decision

PAGE 1009



A mammalian olfactory neuron expresses one olfactory receptor (OR) allele, chosen from the hundreds of OR genes. There is evidence that both OR-gene selection and OR-protein-dependent feedback inhibition play important roles in the allelic exclusion mechanism, but how monoallelic expression is achieved has remained unclear. Here, Nguyen et al. reveal a prominent role for the OR-coding sequences themselves in both exerting and receiving feedback inhibition to ensure expression of a single allele. An OR-coding sequence, when expressed as a transgene under a nonendogenous promoter, is sufficient to suppress expression of endogenous OR-genes and is also sufficient to serve as a target for the feedback inhibition. The findings shed light on a new layer of regulation in OR allelic exclusion.